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British Gynaecological Cancer Society (BGCS) Epithelial Ovarian / Fallopian Tube / Primary Peritoneal Cancer Guidelines: Recommendations for Practice

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The remit of this guideline is to collate and propose evidence-based guidelines for the management of epithelial ovarian-type cancers (ovary, fallopian tube or peritoneal origin) and borderline tumours. This document covers all epithelial cancers with any histological subtype.

Grades of recommendations

Recommendations are graded as per the Royal College of Obstetricians and Gynaecologists document. Clinical Governance Advice No. 1: Guidance for the Development of RCOG Green-top Guidelines, available on the RCOG website at:

https://www.rcog.org.uk/en/guidelines-research-services/guidelines/clinical-governance-advice-1a/

See appendix for more details.

Evidence was searched in the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library 2010, Issue 3), MEDLINE and EMBASE up to August 2014, registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field.

Guideline development process

1) These guidelines are the property of the BGCS and the Society reserves the right to amend/withdraw the guidelines.
2) The guideline development process is detailed below:
    a. Chair, officers, council and guidelines committee (GC) nominated a lead for each guideline topic;
    b. Lead then identified a team called the guideline team (GT) to develop the 1st draft;
    c. 1st draft was submitted to the GC;
    d. GC approved draft and recommended changes;
    e. Changes were accepted by the GT who produced the guidelines;
    f. 2nd draft was then submitted to council members and officers;
    g. Council and officers approved 2nd draft and recommended changes;
    h. Changes were then accepted by GC and GT;
    i. 3rd draft was sent to national and international peer review;
    j. GC and GT then made changes based on peer review comments;
    k. 4th draft was sent back to council for approval;
    l. 4th draft was sent to BGCS members for feedback;
    m. GC and GT then made changes based on members' feedback;
    n. 5th draft was sent to public consultation including patient support groups;
    o. GC and GT then made changes based on non-members' feedback;
    p. Final draft approved by council and officers.

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1. Introduction

Incidence, prevalence and clinical presentation

Epithelial ovarian cancer (EOC) is the 6th most common cancer among women in the UK (2014) and accounts for 4% of all new cases of cancer in females: it has the highest mortality of all gynaecological cancers, accounting for 6% of all cancer deaths in women (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer - heading-Zero). A total of 7,378 new cases were reported in the UK in 2014 (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer - heading-Zero). The crude incidence rate is 23 new ovarian cancer cases for every 100,000 females in the UK, with higher rates in Wales and lower rates in Northern Ireland compared with England. EOC occurs predominantly in post-menopausal women, peaking in the 60-64 years' age group.

Despite the improvements in cancer detection, through increased use of imaging and CA125 measurement, more than 70% of patients with newly diagnosed EOC will present with extra-pelvic, and therefore advanced, disease (FIGO stage-III or IV). Approximately one third of EOC-patients in England presented as an emergency before 2006, with up to 74% of these patients not subsequently receiving any active cancer treatment. (http://www.ncin.org.uk/publications/data_briefings/routes_to_diagnosis). However, rates of emergency presentations have fallen (from 31% in 2006 to 26% in 2013) and two week wait (TWW) referrals have increased significantly (from 22% in 2006 to 31% in 2013). Overall, 36% of EOC patients die within the first year of presentation.(1)

Diagnosis

Presenting symptoms

Symptoms associated with ovarian cancer (particularly when present for more than a year and occurring more than 12 times per month) are persistent abdominal distension, abdominal bloating, early satiety and/or loss of appetite, pelvic or abdominal pain, and increased urinary urgency and/or frequency. Other symptoms may include: postmenopausal bleeding; unexplained weight loss; fatigue or changes in bowel habit.(2)

A number of case–control studies investigating symptoms in women with ovarian cancer and comparing them to symptoms in women without ovarian cancer demonstrate that patients with ovarian cancer are symptomatic for a variable period before diagnosis and challenge the perception of ovarian cancer as the "silent killer".(3)

Diagnostic methods - Current guidance

Sequential testing with CA125 and ultrasound in women presenting to primary care with symptoms suggestive of ovarian cancer is recommended. This is especially so in women over the age of 50. Urgent referral to secondary care is indicated, if both tests are abnormal, or if women present to primary care with a pelvic or abdominal mass.(2)

In the UK, recommendations for diagnosis and referral are based on National Institute for Health and Clinical Excellence (NICE) guidelines on the Recognition and Initial Management of Ovarian Cancer (2) and the Scottish Intercollegiate Guidelines Network guidelines on epithelial ovarian cancer.(3)

The prospective Canadian Diagnosing Ovarian Cancer Early (DOVE) study investigated whether open-access assessment would increase the rate of early-stage diagnosis of ovarian cancer.(4)The analysis of 1455 women demonstrated that DOVE patients presented with less tumour burden than the general population of patients, had significantly lower CA125 levels and attained significantly higher complete tumour resection rates (due to the lower tumour burden) even though no stage shift *per se* was noted. The investigators concluded that because the development of most (high grade serous) ovarian cancers is thought to be extra-ovarian, early diagnosis programmes should ideally aim to identify low-volume disease, rather than early-stage disease, and that diagnostic approaches should be modified accordingly.

2. Screening and prevention

Risk Stratification

Protective factors include combined oral contraceptive pill use, pregnancy, sterilization/tubal ligation and hysterectomy. Factors associated with increased risk include family history associated with mutations in the *BRCA1*, *BRCA2* or mismatch repair genes (Lynch Syndrome), nulliparity or first birth after age 35 years, early menarche, and late menopause.

Primary care

CA125 and pelvic ultrasound scan (+/- TVS as indicated) should be considered the initial investigations for post-menopausal women presenting with signs or symptoms of ovarian cancer (Grade B).

Women with an RMI of ≥250 should have further investigations and be referred to the specialist gynaecological centre MDT (Grade B).

There is currently no role for organized screening programmes in women considered at low risk of development of ovarian cancer (Grade A)

The role of ovarian cancer screening in women at high risk of ovarian cancer has yet to be established (Grade B)

Clinical examination and serum CA125 measurement should be considered in women with symptoms suggestive of ovarian cancer. If the CA125 is ≥35 IU/ml, or if a pelvic mass or other abnormality is identified at examination, an ultrasound scan of the abdomen and pelvis should be considered. For women with a normal CA125 <35 IU/ml, or a CA125 ≥35 IU/ml associated with a normal ultrasound, careful clinical assessment for other causes for their symptoms is required. Women in this group should return to their GP, if their symptoms become more frequent and/or persistent. (2)

The American Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomised Controlled Trial demonstrated that screening asymptomatic postmenopausal women with a single threshold value of CA125 does not result in reduction of mortality, despite 13 years of long term follow up. Diagnostic evaluation following a false-positive screening test result was associated with complications.(5, 6).

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial randomised 202,000 women to observation alone, multimodal screening (MMS), with an algorithm based on serial values of CA125 and follow on transvaginal ultrasound scanning (TVS) for abnormal results, or serial TVS alone. The results showed no reduction in mortality in the primary analysis, but a possible reduction in mortality after exclusion of prevalent cases after 7 years of follow-up. Long-term data and cost-effectiveness data are awaited.(7)

Approximately 1.3% of women in the general population will develop ovarian cancer in their lifetime (4). By contrast, according to the most recent estimates 39% of women who inherit a harmful *BRCA1* mutation (5, 6) and 11-17% of women who inherit a harmful *BRCA2* mutation will develop ovarian cancer by age 70. (8, 9) The UK Familial Ovarian Cancer Screening Study (UKFOCCS) study evaluated a strategy of annual ultrasound and CA125 measurement in 3,653 women considered at >10% risk of development of ovarian cancer and who declined risk-reducing salpingo-oophorectomy (RRSO). The positive and negative predictive values of incident screening were 25.5% (95% CI, 14.3 to 40.0) and 99.9% (95% CI, 99.8 to 100), respectively. This study is still on-going and work up to 2018 will evaluate a 4-monthly screening strategy with CA125 and ultrasound in this group.(10) RCOG guidelines (2015) did not recommend routine screening in these women (https://www.rcog.org.uk/globalassets/documents/guidelines/scientific-impact-papers/sip48.pdf).

Risk-reducing salpingo-oophorectomy (RRSO) prevents development of epithelial ovarian cancer and reduces mortality in women at high risk for epithelial ovarian cancer (Grade B).

Prospective multicentre cohort studies have demonstrated that risk-reducing salpingo-oophorectomy (RRSO) is associated with a lower risk of EOC, first diagnosis of breast cancer, all-cause mortality, breast cancer–specific mortality, and ovarian cancer–specific mortality in BRCA1- and BRCA2-mutation carriers, although there still is a residual risk for peritoneal cancer.(11, 12) On-going studies are evaluating the role of opportunistic salpingectomy in the prevention of ovarian cancer in low risk women.(13)

Tumour markers and Malignancy Indices

Tumour markers are not diagnostic tests, but may be helpful in establishing diagnosis and providing baseline values that may be of use during follow up.(14)

Prospectively acquired evidence from the United Kingdom Collaborative Trial of Ovarian Cancer Screening Cancer (UKCTOCS) - with 46,237 women triaged using MMS in whom serial CA-125 measurements were interpreted via the risk of ovarian cancer algorithm (ROCA®) - has shown that screening by using ROCA® doubles the number of screen-detected EOC compared with a fixed cut off of 35 IU/ml.

Caution must be exercised in reassuring women with a single normal CA125 measurement and a focus more on interpreting trends, along with the clinical picture and imaging findings, is likely to define the standard of care in the future.(15)

3. Secondary care and initial pre- treatment assessment

In women below 40 years of age with suspected ovarian cancer, measure alpha fetoprotein (AFP), and hCG (human Chorionic Gonadotropin), in addition to CA125, to identify women with non epithelial ovarian lesions (Grade C) . Inhibin should be measured at a presumed diagnosis of a granulosa cell tumor, even though logistically it takes potentially longer to access the results.

Secondary care

Following referral of a patient with a mass suspicious of ovarian cancer to secondary care, an expansion of the tumour marker panel may facilitate diagnosis.

Where CA125 is elevated, a preoperative CA125/CEA ratio < 25 , especially in combination with an elevated CA19-9, may indicate peritoneal carcinomatosis from a gastrointestinal tumour and bi-directional gastrointestinal endoscopy should be considered prior to upfront primary debulking surgery.[Grade B]

HE4 (human epididymis protein 4) has shown promising diagnostic and prognostic value in triaging younger women, with HE4 not raised in cases of pelvic inflammatory disease and endometriosis despite CA125 elevation being observed. (16-18)

Large prospective studies from the International Ovarian Tumour Analysis consortium (IOTA) suggest that using simple “M”(malignant) and “B” (benign) ultrasonographic rules to characterise ovarian masses is highly accurate. Using these simple rules, the reported sensitivity for malignancy was 95%, specificity 91%, positive likelihood ratio 10.37, and negative likelihood ratio 0.06. (19) The accuracy of the IOTA ultrasonographic rules has been demonstrated in secondary care, predominantly with specialists in ultrasonography and their wider use remains under evaluation in the UK (http://www.birmingham.ac.uk/rockets). Results from an on-going study to evaluate the best serum diagnostic tests and ultrasound models to detect ovarian cancer are awaited.

Advised examinations prior to deciding treatment

In patients with presumed ovarian cancer, radiological staging will provide further information about the extent of disease and potential distant metastases or secondary cancers. (Grade C)

CT prediction of suboptimal cytoreduction is not sufficiently reliable and in the absence of favourable data from larger, prospective trials should not be used alone to decide management. (Grade B)

MRI should not be routinely used for assessing women with suspected ovarian cancer outside of clinical trials, but can be useful where the results of the USS are not helpful in confirming a

diagnosis, especially in young women with a solitary pelvic mass who want a fertility sparing approach. (Grade B)

PET CT is not recommended for routine preoperative staging in the NHS outside a clinical trial. (Grade C)

CT imaging of the thorax, abdomen and pelvis is recommended to help define the extent of disease and to aid in surgical planning. However, retrospective data have shown that CT cannot accurately predict fine nodule peritoneal carcinomatosis, and therefore mitigate against suboptimal cytoreduction, and that it is not always reliable and reproducible.(2, 20) Current prospective imaging trials are underway to prospectively assess the predictive value of novel imaging techniques in determining operability.

CT has significant value in excluding distant macroscopic disease spread, including intraparenchymal liver or lung metastases and retroperitoneal node involvement, and in excluding synchronous cancers from other sites or thromboembolic events that may alter management. (Grade B)

Current national guidance recommends that MRI should not routinely be used for assessing women with suspected ovarian cancer, but may be used as a problem-solving tool and adjunct to other imaging modalities. There is also no evidence based value in the routine use of specialized imaging techniques such as positron emission tomography–computed tomography (PET CT), although it may be useful as a problem-solving tool in highly specialised situations (for example in the evaluation of thoracic/mediastinal lymph nodes where secondary intra-abdominal debulking for relapsed disease is under consideration).(21)

Diffusion weighted MRI may have a future role in the description of tumour dissemination patterns and assessment of operability, but prospective evidence data for that are warranted.(22)

Cytological/Histological Diagnosis

If offering cytotoxic chemotherapy to women with suspected advanced ovarian cancer first obtain a confirmed tissue diagnosis by histology in all but exceptional cases. (Grade C)(2)

Only commence cytotoxic chemotherapy for suspected advanced ovarian cancer on the basis of positive cytology alone and imaging and without histological confirmation in exceptional cases and where obtaining a tissue sample would be inappropriate. A discussion of such cases at the multidisciplinary team meeting including a careful consideration of the risks and benefits should be documented (Grade C).

All patients with histology / cytology showing suspected or actual carcinoma of gynaecological origin should be reviewed at a gynaecology multidisciplinary team (MDT) meeting.

Histological diagnosis is not mandatory prior to upfront debulking surgery if the clinical picture, imaging and tumour marker profile are highly suggestive of epithelial ovarian cancer (CA125:CEA ratio >25:1).

If ascites is sent for cytological analysis, the absence of malignant cells does not exclude ovarian malignancy, especially in the presence of inflammation (Grade B).(23, 24)

The use of immunohistochemistry on a cell block can be of help in such cases if sufficient atypical cells are present to allow for separation from background cells and interpretation of patterns of staining. This is of high value to aid tissue diagnosis in mixed or undifferentiated tumours.

Where upfront cytotoxic chemotherapy is offered to women with suspected advanced ovarian cancer, histological tissue diagnosis via image guided biopsy or laparoscopy is mandatory in all but exceptional cases. Cytology alone, together with a CA125/CEA ratio of >25:1 may be sufficient in patients with poor performance status (PS 3,4) and where biopsy is not feasible. (Grade C)

In the majority of the cases tissue can be safely obtained through image guided biopsy. The value of laparoscopy in the assessment of operability and impact on overall surgical and clinical outcome of advanced ovarian cancer has not been established in prospective randomised trials . Emerging research protocols utilize laparoscopically obtained multiple intra-abdominal biopsies to define molecular biological profile of each individual patient but the survival benefit of this approach has not been proven in any prospective randomised trials.

The routine use of laparoscopy to obtain pre-treatment histology and to assess the operability of disease is not recommended. (Grade B)

Data to support laparoscopic assessment to determine tumour resectability is limited and suffers from verification bias.(2) In a Cochrane review, assessing the accuracy of laparoscopy to determine tumour resectability in ovarian cancer, only two studies performed laparoscopy and laparotomy in all patients. (25) The other studies only performed a laparotomy when it was thought that an optimal result was feasible. It is therefore not possible to draw definitive conclusions about the sensitivity of laparoscopy. Three studies developed or validated a prediction model including laparoscopy. Using a prediction model did not increase the sensitivity and resulted in more patients undergoing suboptimal surgery**.**

A multidisciplinary discussion within a quorate MDT as constituted along national guidelines is fundamental to the appropriate management of each individual patient and should be documented prior to a decision to operate, offering chemotherapy or palliative treatment in all but exceptional cases, such as emergency presentations between meetings, and the management of these cases should be agreed and described in a departmental gynaecological cancer operational document.

Significance and caveats of cytology

In about two thirds of patients with known ovarian carcinoma, malignant cells are seen in the ascitic fluid. However, there are strong reservations about using peritoneal or ascitic cytology without

histological confirmation in the primary diagnosis of ovarian cancer. Cytological preparations lack architectural patterns and false positive tests may be obtained from serous borderline tumours and from exfoliation of other cells, such as epithelial cells from Müllerian rests and reactive mesothelial cells, which may be mistaken for carcinoma. This problem may be partially resolved through constructing cell blocks and performing appropriate immunohistochemistry, but despite this, the use of cytology in the diagnosis of ovarian carcinoma has a high false negative rate and is operator dependent.

Histological confirmation is recommended prior to treatment with chemotherapy. In exceptional cases, where obtaining material for histology is not possible or is associated with a high risk due to the poor performance status or co-morbidities of the patient, cytology may be used alone in establishing a pre-chemotherapy diagnosis.

In women with pleural effusions, aspiration and examination for malignant cells and cytology should be considered to confirm staging (preferably with immunohistochemistry on cell block). (23, 24).

When used in trial settings, cytological preparations are suboptimal for archiving, tissue microarrays and some molecular testing.

4. Pathology and genetics

The provision of a minimum set of clinical information on the histopathology request form is crucial to ensure a histopathology report of high enough quality for the accurate diagnosis and appropriate management. (Grade D)

Frozen section may be performed, if the result will alter the intra-operative management although there are limitations to the technique. (Grade B)

Clinical information required on the specimen request form

The Royal College of Pathology guidelines for reporting ovarian carcinomas mandate the provision of minimum clinical details to include demographics, clinical presentation, results of previous biopsies, radiological investigations for tumour staging, and details of the surgical procedures performed. It is desirable to include details of any family history of cancer and relevant hormonal therapy. The nature of surgical specimens from multiple sites should be carefully recorded and the specimen pots labelled to correspond to the specimen details on the request form and appropriately labelled as to site of origin.

Primary site assignment

The origin of high-grade serous ovarian carcinoma (HGSC) has been the subject of intense study. The distal fallopian tube has emerged as the likely site of origin for most HGSC. (26) This observation is, in great part, attributable to the use of sampling protocols that thoroughly examine the distal fallopian tube and also due to the greater number of specialist pathologists with a sub-specialty interest in gynaecological pathology. The discovery of serous tubal intraepithelial carcinoma (STIC) in women with BRCA1 or BRCA2 mutations following risk-reducing salpingo-oophorectomies (RRSO) and in women with advanced ovarian carcinoma lead to the hypothesis that the natural history of pelvic

HGSC might involve an origin in most cases of the distal fimbria of the fallopian tube. Identification of STIC in 18% to 60% of cases of advanced/symptomatic HGSC supports this assertion. STIC lesions are characterized by DNA damage, TP53 mutation, and progressive molecular abnormalities that are also seen in high-grade serous carcinoma. An origin from epithelial inclusion cysts in the ovary has been proposed as a potential explanation as site of origin in the cases where complete examination of the fallopian tube does not reveal STIC. A consensus statement on primary site assignment in tubo-ovarian HGSC has been made. (27)

Immunohistochemical features of HGSC

HGSC of tubo-ovarian and peritoneal origin have similar morphological and immunohistochemical features. HGSC can be arranged in papillary, glandular or solid architecture. HGSC exhibits moderate to marked nuclear atypia and greater than 12 mitoses per 10 high power fields. Necrosis and multinucleate cells are often present. The distinction between low-grade and high-grade serous carcinoma is based on cytological, not architectural, features. On immunohistochemistry, HGSC of tubo-ovarian and peritoneal origin are typically positive for CK7, WT1, PAX8, oestrogen receptor and CA125. They do not stain for CK20, CEA and CDX2. P53 shows aberrant expression, characterized by either diffuse strong positive staining in greater than 75% of cells or by complete lack of staining.

Genetics

Women with HGSC or G3 endometrioid ovarian adenocarcinoma have >10% risk of an underlying BRCA mutation and should be offered clinical genetics counselling and testing. (GRADE C)

Recently it has been shown that ~18% (much higher in certain groups such as Ashkenazi Jews) of the population of women presenting with high grade serous or G3 endometrioid ovarian adenocarcinoma carry a germline BRCA mutation, 44% of whom have no positive family history.(28) Every patient with a current or past histological diagnosis of HGSC or G3 endometrioid ovarian carcinoma therefore qualifies for BRCA counselling and testing, as advised by NICE, which should be discussed and offered .(29) The advantages of BRCA testing include:

- Prognostic information, as this group is likely to have longer remission periods;
- Predictive genetic testing and advice for other family members who are at risk of inheriting BRCA, about screening and risk-reducing surgery to minimise their chance of developing cancers;
- PARP inhibitor treatment may offer longer-term remission and response for some BRCA-mutation carriers. (30) Olaparib is an option for treating women with relapsed, platinum-sensitive ovarian cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum-based chemotherapy, if they have had 3 or more courses of platinum-based chemotherapy. (31)

Special histological features of different subtypes

Endometrioid Carcinoma of ovary

These represent the second most common form of ovarian EOC and account for 10 – 15% of ovarian EOC. A significant number are associated with endometriosis in the ovary, or elsewhere in the pelvis,

and about 15% of cases have synchronous endometrial carcinomas. (32, 33) Endometrioid carcinomas of the ovary can show a variety of patterns of which an adenofibromatous pattern and squamous metaplasia are amongst the confirmatory endometrioid features. The clinical management of G3 endometrioid ovarian cancers corresponds to that described for high-grade serous cancer (HGSC).

Clear cell carcinoma

Clear cell carcinoma is the subtype most frequently associated with pelvic endometriosis, paraneoplastic hypercalcaemia and venous thromboembolism. The tumour is composed of clear, or hobnail, cells arranged in papillary, glandular or solid patterns in a hyaline stroma. The cells are typically WT1-/p53 wild type and show staining with napsin A. They mostly lack expression of oestrogen and progesterone receptors.(34) Clear cell carcinoma of the ovary is managed in an identical manner to HGSC, but is less responsive to chemotherapy than serous and endometrioid histological subtypes.

Carcinosarcoma

Carcinosarcoma is a rare gynecological neoplasm that may arise in any region of the gynaecological tract and which accounts for 1% to 3% of ovarian cancers. It belongs to the category of mixed Müllerian tumours, with both epithelial and mesenchymal components being malignant. They were previously called malignant mixed Müllerian tumours (MMMT). Recent immunohistochemical and molecular findings support the hypothesis that gynecological carcinosarcomas represent metaplastic carcinomas. Cell lines established from carcinosarcomas are able to differentiate into epithelial or mesenchymal components, or a combination of the two, (35) and immunohistochemistry demonstrates the expression of epithelial markers in the sarcomatous component of carcinosarcoma. Clonality patterns, genomic analysis, and loss of heterozygosity studies have shown that carcinomatous and sarcomatous components of these tumours share common genetic alterations, including aberrant p53 expression and occasionally germline mutation of BRCA2.(36, 37) The transformation of a carcinoma to a sarcoma in these tumours may represent a transdifferentiation, as seen in epithelial-to-mesenchymal transition phenomena. (38)
Overall, the prognosis for carcinomosarcoma is worse than for high-grade ovarian carcinoma of a similar FIGO stage (39). Most (90%) present with advanced disease. At present they should be managed in the same way as HGSC.

5. Surgical treatment

Suspected or Confirmed Early Stage Disease

Women with suspected epithelial ovarian cancer should undergo surgery at a cancer centre by specialised surgeons who are core members of a specialist MDT. (Grade B)

Women requiring chemotherapy should be treated by a medical or clinical oncologist who is a core member of a specialist MDT. (Grade D)

Affected women should have an identified key worker and responsible clinician. (Grade D)

Treatment summaries, including symptoms of recurrence, should be provided to all women on completion of each episode of treatment and on discharge to primary care. (Grade D)

The aim of surgery for early ovarian cancer (stage I and II) is complete macroscopic tumour resection and adequate surgical staging. (Grade A)

Patients suitable for fertility-sparing surgery should be identified by the MDT and the pros and cons of this discussed with them, so that they can make an informed choice. (Grade D)

Early stage disease may be an unexpected post-operative histological finding in cases that have been managed as a benign condition. A re-staging procedure by a gynaecological oncologist could be advised to establish stage and possibly define type or necessity of adjuvant treatment (Grade B).

Adequate (non fertility-sparing) primary surgery for apparent early stage ovarian cancer consists of peritoneal washings/ascitic sampling taken prior to manipulation of the tumour, bilateral salpingo-oophorectomy, total hysterectomy, multiple peritoneal biopsies from the para-colic spaces, and the sub-diaphragmatic spaces bilaterally, omentectomy, and pelvic and bilateral para-aortic lymph node assessment up to the level of the insertion of the ovarian vessels in the absence of peritoneal dissemination. (Grade B)

The rate of positive lymph nodes in mucinous tumours is very low and lymph node dissection is therefore not warranted. However, appendicetomy should be performed where a mucinous tumour is suspected. (GRADE B)

Women with suspected ovarian cancer should be referred to gynaecological oncology centres for treatment. A meta-analysis of retrospective studies assessing over 9000 women suggested that treatment of women in institutions with gynaecological oncologists on site may prolong survival, compared to community or general hospitals (HR 0.90; 95% CI 0.82 to 0.99)(40) This supports guidelines in the UK on Improving Outcomes in Gynaecological Cancers (41, 42).

Full surgical staging provides useful prognostic information and may affect subsequent treatment. The survival value of full surgical staging in apparent stage I ovarian cancer is extrapolated from data from RCTs assessing the benefit of adjuvant chemotherapy in early stage disease (43,44).

Depending on the histological grade and subtype, up to 30% of the patients with apparently early epithelial ovarian cancer will be upstaged after comprehensive surgical staging. (46, 47) Cass and colleagues showed in 96 patients with grade 3 tumours and gross disease confined to one ovary, that 15% had microscopically positive lymph nodes. (48) Among these patients, 50% had positive pelvic nodes, 36% had positive para-aortic node and both were positive in 14% of the cases. Maggioni and colleagues reported on a prospective randomised trial of systematic lymphadenectomy in patients with ovarian cancer macroscopically confined to the pelvis. Positive nodes were detected in 22% of patients undergoing systematic lymphadenectomy compared to only 9% of patients who underwent merely a sampling (p=0.007). Although a trend for improved PFS and OS was observed for the lymphadenectomy group compared to control, the study lacked the statistical power. (49) Increasing evidence shows that the rate of positive lymph nodes in stage I mucinous cancer is extremely low

(near 0%), and there is no value in performing this given the potential morbidity of such the procedure. (50-52)

When young women are affected by early stage epithelial ovarian cancer, fertility-sparing surgery can be considered following thorough discussion with the patient about the potential risk of recurrent epithelial ovarian cancer. Patients with grade 1 or 2 mucinous, serous, endometrioid, or mixed histology and FIGO stage IA or stage IC with unilateral ovarian involvement may be eligible for uterus/contra-lateral ovary preserving surgery, in combination with surgical staging of the remaining peritoneal surfaces +/- retroperitoneal lymph node chains (dependent upon histological subtype). In a large retrospective analysis, women with G3 disease or stage IC3 with clear cell histology had a higher risk of recurrence, but mainly related to the higher incidence of extra-ovarian spread observed in grade 3 tumours, rather than to a higher relapse rate in the preserved ovary.(53) Therefore, these patients should be carefully informed about their prognosis, to enable them to make a personalized and informed choice. Retrospective evidence reveals that 3.5%-11% of the women with unilateral disease will have contra-lateral pelvic lymph node metastases, despite negative ipsilateral nodes. (54, 55)

Surgical management of primary advanced ovarian cancer

Surgery after three cycles of chemotherapy following initial low effort or diagnostic-only surgery significantly lengthens progression-free and overall survival in patients with advanced disease compared to no further surgery. (Grade A)

A "second look" operation with cytoreductive attempt after neo-adjuvant chemotherapy following upfront debulking surgery with residual disease despite maximal effort has no survival benefit and is not recommended (Grade A).
The aim of cytoreductive surgery in the management of advanced stage ovarian cancer is surgical resection of all visible disease in patients fit enough to undergo this procedure, as this has been shown to be associated with an improved progression-free and overall survival. (Grade B)

Neo-adjuvant chemotherapy with interval debulking surgery after three cycles of platinum based chemotherapy is non-inferior to primary upfront debulking surgery and adjuvant platinum-based chemotherapy and has reduced morbidity in patient cohorts with significant disease burden and low complete macroscopic tumour clearance rates or in situations where the is uncertainty about the possiblity of optimal removal of tumour (Grade A)

Women with advanced disease should have their treatment planned by a specialist MDT at cancer centres having the infrastructure to support maximal surgical effort debulking with the aim of no macroscopic residual disease. (Grade D)

Bulky lymph nodes in advanced disease should be removed, if this will complete macroscopic clearance, as this has been shown to significantly prolong survival and is part of the debulking. (Grade A)

In advanced epithelial ovarian cancer the aim is complete cytoreduction of all macroscopically visible disease, since this has been shown to be associated with a significantly increased overall and progression-free survival in numerous prospective and retrospective trials. (56-58)
It is unclear whether this association is causal or whether resectable tumours are intrinsically biologically more chemosensitive and less likely to recur quickly.(59-61) The only evidence comparing maximal effort debulking surgery versus no further surgery is in the setting of interval debulking surgery. The EORTC trial by van der Burg et al, which randomised 319 patients to further surgery versus no surgery followoing three cycles of platinum-based chemotherapy after initial surgery by a non-gynaecological oncologist or diagnostic surgery only.(57) The study, and subsequent Cochrane review which included three studies, showed that interval debulking surgery lengthened progression-free and overall survival only in those who had not had maximal effort at initial surgery. (62) The risk of death was reduced by one third in this subgroup, after adjustment for a variety of prognostic factors (HR = 0.68, 95% CI 0.53 to 0.87, I^2 = 0%).(62)

In order to achieve macroscopic tumour clearance in peritoneally disseminated disease, maximal surgical effort is required, potentially including multi-visceral resection techniques such as peritoneal stripping, diaphragmatic resection, removal of bulky pelvic/ para-aortic lymph nodes, splenectomy, liver and/or liver capsule resection and bowel resection. Retrospective data suggest that additional surgical procedures do result in improved rates of cytoreduction. This requires specialist training and surgical expertise, as well as co-ordinated institutional effort to safely deliver.(63) Therefore women with advanced disease should ideally undergo such surgery in specialized centres with adequate infrastructure, staff and training. (64) These centres should consider keeping prospective records of the surgical and non-surgical management of all patients, the surgical procedures performed, the amount and location of any residual disease and associated morbidity and mortality. Surgery should be ideally performed within 2-4 weeks of decision to operate, depending on patients' wishes, co-morbidities and prior history.

The Chief Medical officer has emphasised the need for specialist surgical training and the need for a national audit in ovarian cancer to improve outcomes. (65) The on-going SOQCER2 study should give further information about the quality of life after debulking surgery.
(https://clinicaltrials.gov/ct2/show/NCT02569983).

Complete macroscopic cytoreduction is defined as macroscopic tumour clearance with no residual visible disease, as documented by a comprehensive visual assessment of all the areas of the abdomen. When complete macroscopic cytoreduction is not achievable at the time of laparotomy, attempts should be made to achieve near-optimal cytoreduction (<1cm residual disease) as meta-analysis suggests that patients in whom <1cm residual disease remains have a greater overall survival than those with >1cm residual disease, if associated morbidity seems acceptable and depending on the constitution of the patient. (56)

The value of systematic pelvic and para-aortic lymphadenectomy in advanced disease in the absence of bulky lymph nodes has not been prospectively proven to influence overall survival**.** A large prospectively randomised trial that randomised patients with residual disease <1cm to removal of bulky lymph nodes only versus systematic pelvic and para-aortic LND showed that 5-year PFS could

be improved in the systematic LND arm; from 21.6% to 31.2% with a median of an additional seven months. (66) The study failed to show any overall survival benefit from a systematic LND. A large multicentre prospectively randomised trial of systematic pelvic and para-aortic lymphadenectomy extending up to the renal vessels in tumour free operated patients with advanced disease and without bulky lymph nodes has completed accrual (LION Trial, AGO-OVAR OP.3 [NCT00712218]) and the results are awaited in ASCO 2017.

There is no proven value or survival benefit in second look cytoreductive surgery after three cycles of chemotherapy to clear any disease remaining after primary surgery performed with maximal surgical effort unless this paradigm was not employed upfront. (62) Similarly, a "second look" diagnostic laparoscopy or laparotomy after completion of treatment to assess intra-peritoneal status should not be routinely performed, except in the context of pertinent clinical trials, as its impact on survival has not been demonstrated. (67)

6. Systemic treatment of early stage ovarian cancer (FIGO I-II)

Adjuvant platinum-based chemotherapy should be discussed and offered in all cases of early ovarian cancer apart from low grade stage Ia/Ib. (Grade A)

Two randomised, prospective trials examined the value of chemotherapy after surgery in early stage ovarian cancer. The ACTION and ICON1 trials included early stage cases, with grade 2/3 stage IA/B and all stage IC/IIA eligible. The primary analysis of ICON1, with a median follow-up of four-years, demonstrated a significant improvement in both relapse-free survival (RFS) (Hazard Ratio (HR)=0.65, 95%CI=0.46-0.91, p=0.01) and overall survival (OS) (HR=0.66,95%CI=0.45-0.97,p=0.03) in favour of adjuvant chemotherapy with six cycles of single agent carboplatin (AUC 5/6). (68) Similar findings were reported in the ACTION trial in which the majority of patients received platinum-based combination chemotherapy. (69)

A Cochrane meta-analysis of five large prospective clinical trials concluded that chemotherapy is more beneficial than observation in patients with early stage ovarian cancer. (70) Patients who received platinum-based adjuvant chemotherapy had a better OS (hazard ratio (HR) 0.71; 95% confidence interval (CI) 0.53–0.93] and PFS (HR 0.67; 95% CI 0.53–0.84) than patients who did not receive adjuvant treatment. Approximately two thirds of the cases were sub-optimally staged and 30% of women with presumed stage 1 disease may have had undetected stage 3 disease. One interpretation is that the observed effect is due to the overuse of chemotherapy in cases unlikely to benefit compensating for the lack of complete surgical staging. However, due to concerns with outcome reporting bias, the Cochrane review performed an analysis of 10-year data from ACTION and ICON1, which suggested that the difference between optimally and sub-optimally staged subgroups, in terms of deaths from ovarian cancer, was not significant (Test for subgroup differences: Chi^2 test = 2.75, df = 1, P = 0.10). Benefit for chemotherapy, even in optimally staged patients, could not be excluded. Adjuvant chemotherapy should be discussed with all patients with high risk early stage ovary cancer.

There is a lack of evidence supporting an additional value of targeted therapies such as bevacizumab, other VEGF inhibitors including nintedanib and cediranib, tyrosine kinase inhibitors or PARP inhibitors in early stage ovarian cancer treatment and show they should not be offered outside clinical trials. (Grade D)

The response rate to chemotherapy in patients with non-serous epithelial ovarian carcinoma, including clear cell and mucinous tumours, is poor and the effectiveness of adjuvant chemotherapy in early stage disease in these groups may be less than HGSC. However, as patients with non-HGSC subtypes were not excluded from previous studies and, since there are currently no evidence-based alternatives for women with non-HGSC subtypes, it is remains reasonable to offer treatment as per HGSC. Women with non-HGSC should be encouraged to participate in histological subtype specific studies, where these exist.

7. First-line chemotherapy for advanced disease (FIGO II – IV)

Neoadjuvant chemotherapy

Primary debulking surgery is the standard of care where complete or optimal cytoreduction appears achievable in patients with good performance status. Where this is not achievable two randomised trials have showed non-inferiority of the neo-adjuvant chemotherapy (NAC) followed by interval debulking surgery. Both trials demonstrated reduction in morbidity in the NAC arm and an equal quality of life in both arms. (Grade A)

Two prospectively randomised trials have shown that treating patients with advanced ovarian cancer with NAC followed by interval surgery after three cycles is no worse than first-line surgery. (58,72), especially in cases where performance status and/or resection is unlikely to result in an optimal debulking procedure and that this strategy is associated with lower surgical morbidity and mortality in this context. The limiting factor of both studies was that for many atients entered there was uncertainty about the ablity to resect tumour. 'Ability' to optimally resect disease relies in general not just on the actual surgical skills, but also the overall infrastructure, team effort, anesthetic cover and institutional expertise. Both options –upfront surgery and NAC- may be discussed with patients with advanced disease and treatment decisions made based on the patient's performance status, symptoms, co-morbidities, patient preference and quality assured institutional expertise.

A Chemotherapy Response Score (CRS), based on pathological evaluation material prior to NAC and following it has been developed in a single centre but not yet validated in a prospective multicentre setting. The three-tier CRS system applied to omental samples from this initial single centre study showed high reproducibility (kappa, 0.67) and predicted PFS. The score also predicted sensitivity to first-line platinum therapy. Until validation studies are completed and the clinical benefit of the CRS is defined, no recommendation of its routine can be made. (74)

Intra-peritoneal chemotherapy

Intra-peritoneal (IP) chemotherapy can be offered within clinical trials where appropriate expertise and resources exist.

A Cochrane review of IP versus intravenous (IV) chemotherapy demonstrated an improved overall survival if women received an IP component to chemotherapy (eight studies, 2026 women; HR = 0.81; 95% confidence interval (CI): 0.72 to 0.90). Intraperitoneal chemotherapy prolonged the DFI (five studies, 1311 women; HR = 0.78; 95% CI: 0.70 to 0.86). However, there was greater serious toxicity with regard to gastrointestinal effects, pain, fever and infection, but less ototoxicity with the IP than the IV route. (75) The improved survival with IP chemotherapy impact has been shown to extend even beyond 10 years. (76) However, because of concerns over potential toxicity, due to the increased dose of chemotherapy given in some of the IP arms and IP catheter-related complications, it has not been widely adopted in Europe and is currently the subject of on-going trials the results of which are eagerly awaited. Meta-analysis of the current trial data suggests that research is still needed to determine the optimal agent, dose and scheduling and also the value of IP therapy in the era of targeted maintenance tretaments. (77)

Post operative cytotoxic chemotherapy

The current standard of care in advanced disease is carboplatin (AUC5/6) and paclitaxel (175mg/m^2) three-weekly for 6 cycles. (Grade A)

Following surgery, all patients with FIGO stage II-IV ovarian cancer should be offered platinum based chemotherapy +/- paclitaxel, depending on fitness. The interpretation of the results of trials that added paclitaxel to platinum-based drugs during the 1990s generated some controversy, but a meta-analysis showed superiority of the combination of platinum-paclitaxel to platinum-based drugs (79). Carboplatin is less toxic than cisplatin and equally effective. The standard of care is three-weekly carboplatin (AUC5/6) and paclitaxel (175mg/m^2) for six cycles.

Dose-dense scheduling of the paclitaxel (80 mg/m^2 days 1, 8, 15 every 21 days, with carboplatin AUC 5/6 on day 1) has been shown to improve overall survival in a Japanese population. (80) A European phase III trial (MITO7), which randomised patients to standard dose three-weekly carboplatin /paclitaxel or weekly carboplatin (AUC 2) and paclitaxel (60 mg/m^2), showed no difference in PFS or OS, although weekly treatment was better tolerated. (81) An absence of benefit of dose-dense therapy may have been due to the lower dose of paclitaxel (60 mg/m^2 as opposed to 80 mg/m^2 weekly) used in this study. The ICON 8 trial, currently in follow up, has randomised over 1500 patients to receive either three-weekly carboplatin / paclitaxel, three-weekly carboplatin and weekly paclitaxel (80mg/m^2), or weekly carboplatin (AUC 2) and weekly paclitaxel (80mg/m^2) with results expected during 2017.

The addition of a third cytotoxic agent or more than six cycles has failed to show any survival benefit in prospectively randomised trials and is not recommended. (Grade A) (82, 83)

For those patients who develop allergy to or do not tolerate paclitaxel, the combination of protein-bound paclitaxel (Abraxane)-carboplatin or pegylated liposomal doxorubicin-carboplatin could be considered as alternatives. (Grade B) (84, 85)

Hypersenstivity to carboplatin may occur, in which case desensitisation regimens can be useful**,** or the equally efficacious, but potentially more toxic, agent cisplatin can be used as an alternative. Cross-hypersensitivity to cisplatin may occasionally occur.(86)

Anti-angiogenics in adjuvant first-line treatment of ovarian cancer

Targeted therapies, in addition to the conventional first line cytotoxic chemotherapy, have been shown to increase PFS, but not OS, when given as maintenance therapy. The addition of anti-angiogenic therapy increases toxicity. (Grade A)

Giving bevacizumab plus chemotherapy and then alone as maintenance for up to 12 months (ICON 7) (87) or for 15 months (GOG 218) (88) following cytotoxic chemotherapy has been shown to prolong PFS in patients with advanced disease. The three-arm randomised ICON8B trial opened in 2015, building on the ICON8 trial (NCT01654146) to explore the interaction between three-weekly chemotherapy with bevacizumab (ICON7), carboplatin and weekly paclitaxel, and the addition of bevacizumab to weekly paclitaxel.

The addition of other anti-angiogenic agents, including the oral tyrosine kinase inhibitors pazopanib and nintedanib, has also been shown to increase PFS, but not OS. Pazopanib maintenance therapy provided a median improvement in PFS of 5.6 months (HR 0.77; 95% CI 0.64 to 0.91; P = .0021; median, 17.9 v 12.3 months) in patients with advanced ovarian cancer who had not progressed after first-line chemotherapy in a large multicentre phase III study, but with increased treatment-related Grade 3 or 4 adverse events. The schedule has not been submitted for EMA licensing. (90) Nintedanib in combination with carboplatin and paclitaxel has also been demonstrated to be an active first-line treatment that increases PFS in a recent large multicentre phase III trial, but is associated with more gastrointestinal adverse events. (91)

First-line chemotherapy in non-serous histological subtypes

Currently no evidence to support the use of drugs other than platinum-taxane for non-serous histological subtypes (Grade A)

The efficacy of conventional chemotherapy in rarer histological subtypes, including low-grade endometrioid and mucinous subtypes, has been shown to be less effective.(92) Nevertheless, all large phase III randomised chemotherapy trials so far have included all histological subtypes. It has been difficult to conduct randomised trials in rarer histological subtypes. However, a Japanese-led trial in clear cell cancer has recently been published, showing no difference between standard chemotherapy and cisplatin-irinotecan. (93)

In mucinous tumours, an even rarer subtype, an international randomised trial was abandoned due to poor accrual. Currently there is no evidence to support the use of drugs other than carboplatin/paclitaxel in these histological subtypes. Furthermore the role of adjuvant conventional chemotherapy in early stage tumours with rare histological subtypes remains unclear. Currently, decision-making is often based on larger trials that contain patients with these subtype tumours.

The national prospective observational study of rare neoplasias of gynaecological origin (RANGO) will allow the collection of information about tumours in the future. In time, this project will link in with an international Gynaecological Cancer Inter-Group mega-database initiative.

8. Follow-up

A careful history, assessment of new and potentially tumour-related symptoms and clinical examination is essential at follow up visits. (Grade C)

CA125 measurement is not mandatory and has not been proven to be of survival benefit. (Grade A)

Patients should have the contact details of their key worker so that they access an early review for unexpected symptoms. (Grade D)

Follow-up along a traditional hospital-based model provides opportunities to assess the risk and/or presence of recurrence and to assess patients holistically for the presence of on-going physical, psychological, emotional, financial and sexual survivorship issues related to their cancer treatment.

The intervals between follow-up visits vary according to local practice, but the most common schedule through convention is every 3 months for the first 2 years and then every 6 months up to 5 years after end of treatment, despite a lack of randomised trial data illustrating a benefit of strict follow-up protocols over an individualized patient- and symptom-led approach.

Increases in CA125 may herald progressive disease in patients who achieve a normal CA125. A prospectively randomised MRC/EORTC trial demonstrated no difference in overall survival after a median follow-up of 56.9 months (HR 0.98, 95% CI 0.80 to 1.20; P = 0.85) between patients who received chemotherapy based on a rising CA125 and those who did not receive chemotherapy until they were symptomatic. Treatment based on an abnormal CA125 led to early treatment by a median of 4.8 months. (94), (95). Interestingly, those in the arm where treatment was initiated on CA125 rise had a shorter interval to deterioration in global health score or death (HR 0.71, 95% CI 0.58 to 0.88; P value < 0.01). This finding led to many questioning the clinical and cost-effectiveness of routine CA125 measurements in follow-up. Despite this, some patients may wish to know what might lie ahead and for some a rise in CA125 might indicate surgically-resectable disease recurrence, while for others it may trigger imaging that will determine timing and value of further treatment (96). In addition, participation in first-line trials normally requires regular post-treatment CA125 measurements for trial end points. However, it is now accepted that a rising CA125 alone, without clinical or radiographic evidence of recurrence, should not be routinely be used as an indication to commence systemic chemotherapy**.**

The results of the prospectively randomised DESKTOP III (NCT01166737) and GOG 0213 (NCT00565851) trials may potentially change current follow up recommendations, if secondary debulking surgery is shown to be associated with improved survival and becomes a standard of care. Emerging maintenance therapies such as immunotherapy may also require changes in current follow up arrangements in the future.

9. Management of recurrent disease

Surgical treatment of recurrent disease

Cytoreductive surgery could be offered to patients with platinum-sensitive ovarian cancer relapse where the disease appears completely resectable in patients with a good performance status, as this has shown to be associated with improved OS and PFS in retrospective studies and meta-analyses; patients should however be aware that the disease will remain chronic, and that no prospective trials have yet proven a survival benefit. (Grade C)

Palliative surgery for bowel obstruction could be discussed after failure of conservative treatment and after careful consideration of the patient's overall prognosis, quality of life, previous treatments, future therapeutic options and co-morbidities. Iatrogenic induced short bowel syndrome with the necessity of long life total parenteral nutrition should be avoided and plans for surgery should be agreed within a specialist MDT. (Grade C)

The value of surgery for relapsed ovarian cancer on overall survival in patients with EOC has not yet been established in prospectively randomised trials, but when complete tumor removal can be achieved, retrospective studies have shown a significantly longer OS and PFS when compared to women with residual disease following surgery for relapse. This survival benefit persists even in multifocal relapse and peritoneal carcinosis as long as complete tumor clearance is achieved (97-100).

Careful consideration of cases within a specialist MDT can identify individuals whose disease may benefit from a surgical approach. In a large, retrospective, systematic trial (DESKTOP I), patients with two out of three of complete resection at first surgery, good performance status and absence of ascites, had an improved survival. (97) No RCT-level data were identified in systematic reviews. (101, 102) Four prospective multicentre randomised trials evaluating the value of surgery at relapse are now underway: DESKTOP III [NCT01166737] used the selection criteria detailed above and is in follow up, GOG 213 [NCT00565851] incorporates the addition of bevacizumab to chemotherapy, SOC1 [NCT01611766] from the Shanghai Gynecologic Oncology Group, and the SOCceR from the Netherlands [NTR3337]. The results of these prospective trials will define the value of cytoreductive surgery at relapse.

EOC patients often present with symptoms of acute or sub-acute bowel obstruction at relapse, often attributable to diffuse peritoneal dissemination of recurrent tumour rather than a single point of obstruction. The implementation of novel targeted therapies with anti-angiogenic potential may favour fistula formation or intestinal perforation and so recurrent EOC, with the potential to be complicated by such severe and acute events, constitutes a therapeutic dilemma.(103) No RCTs exist comparing surgical and medical management, and evidence that showed a benefit to surgery over octreotide was of low quality. (104) In a retrospective review of 90 patients who underwent surgery for bowel obstruction in relapsed ovarian cancer, the median OS was 90.5 days (range, <1 day-6 years). (105) Palliative surgery in patients with gastrointestinal and other symptoms of ovarian cancer recurrence therefore requires multidisciplinary consideration.(100, 105) Any perceived benefits should be carefully balanced against the risks for each individual patient and factors such as

co-morbidities, baseline quality of life, previous response to chemotherapy, length of treatment intervals and patient wishes are likely to be crucial. The management of these cases should be led by specialist gynaecological multidisciplinary teams, including palliative care input at an early stage. If surgery is planned, intra-operative input from gynaecological oncologists is important, so that likelihood of chemotherapy responses after palliative surgery is considered when making intra-operative decisions.

Endoscopic techniques, such as placement of intestinal stents and percutaneous endoscopic gastrostomy (PEG), may allow the palliation of gastrointestinal symptoms with reduced procedure-related morbidity in selected patients.

Surgical intervention should be restricted to cases where there is a distal mechanical bowel obstruction and where the formation of a proximal high output small bowel stoma is not likely to be necessary, as such high output stomas significantly reduce quality of life and require permanent total parenteral nutrition (TPN). Pre-operative imaging demonstrating the most proximal point of bowel obstruction should be used to identify patients with a level of obstruction at high risk of iatrogenic short bowel syndrome. Management of patients with bowel obstruction should ideally happen within multi-disciplinary teams with experience in managing such cases. (106)

Systemic treatment of recurrent disease

In patients with longer treatment free intervals (TFI) (> 6 months), combination therapies with platinum re-challenge are recommended. (Grade A)

In patients with short TFIs (<6months) single agent therapy is equally effective and less toxic than combination therapies. (Grade A)

Along with patient factors, including patient choice and performance status, residual toxicities and prior hypersensitivity reactions, the most important factors that inform the choice of chemotherapy for relapsed ovarian cancer are the TFI and platinum-free interval (PFI). The conventional definition of platinum sensitivity is a PFI of greater than six months after cessation of the last platinum-based chemotherapy course and was based on the likelihood of disease response to platinum re-treatment in older studies. (107, 108) However**,** in an era of more accurate imaging techniques and maintenance regimens, this definition is more complex with the conventional definition of platinum-sensitive disease becoming less useful clinically (Table 1). (109)

Table 1 The Gynecologic Cancer Intergroup (GCIG) (162) categorisation of patients based on the length of remission following platinum-based chemotherapy. The platinum-free interval is however somewhat theoretical and in real-life exists as a spectrum

Classification	Definition
Platinum Sensitive (PS)	Progress with an interval of > 12 months after completion of chemotherapy
Partially PS (pPS)	Progress with an interval of between 6-12 months after completion of chemotherapy
Platinum Resistant (PR)	Progress with an interval of less than 6 months after completion of chemotherapy
Platinum Refractory (PRef)	Progress during, or within 4 weeks after completion of chemotherapy

While the duration of response to platinum is important, retrospective data also suggest that seeking to extend the platinum-free interval itself may also help improve the patient's subsequent response to platinum re-treatment and there are now several studies supporting this concept.(110, 111) In patients with platinum-sensitive or partially platinum-sensitive ovarian cancer recurrence (6-12 months PFI) published clinical evidence reports response rates to second-line therapy ranging between 27% and 33%, regardless of whether platinum-based or non-platinum drugs are used. However, response rates can be a poor measure of benefit, which is better expressed in terms of PFS and combination therapy (such as carboplatin / paclitaxel, carboplatin / liposomal doxorubicin or carboplatin / gemcitabine) would be recommended as this improves PFS and OS in this group of patients. (107, 112, 113) Trabectedin and pegylated liposomal doxorubicin (PLD) have been shown to be more beneficial compared with PLD alone, especially in the group of patients with partially platinum-sensitive disease. The addition of bevacizumab to relapse chemotherapy in the platinum sensitive setting and as maintenance afterwards also increases PFS compared with combination carboplatin / gemcitabine alone (85, 114).

In the platinum refractory / resistant setting there does not appear to be any advantage in using combination therapies, which are associated with higher rates of adverse events. In the platinum-resistant setting, second-line single-agent chemotherapy with non-platinum drugs (such as PLD, weekly paclitaxel, etoposide or topotecan) results in short-lived response rates of approximately 10% to 25% and PFS of 4-5 months and OS of 12-13 months (96). However, the addition of bevacizumab to conventional chemotherapy has been shown to increase PFS to 6.7 months, with OS of 16.6 months compared to monotherapy (PLD, weekly paclitaxel or topotecan) and improved patient-related outcomes in a carefully selected population (115). If the patient cannot tolerate chemotherapy and/or symptoms are not requiring a rapid response to chemotherapy, then hormonal treatment could be an alternative, although evidence for benefit is limited. (116, 117)

Palliative radiation may have a role in highly selected situations.

10. Other epithelial histological subtypes

Low Grade Serous Ovarian Cancer (LGSOC)

Surgery is the most effective management for LGSOC, which has a lower response rate to chemotherapy than HGSOC. (Grade B)

There is a 25% response rate seen with a platinum-taxane regimen in LGSOC and given the lack of a superior alternative chemotherapy regimen, this can be offered in patients with advanced disease.(Grade B)

LGSOC constitutes about 5% of all serous carcinomas, occurs in younger women and is characterised by a uniform population of cells arranged typically in papillary clusters and showing sparse mitotic activity (118). Neither necrosis nor P53 mutation are features of LGSOC. (119)

The management of LGSOC is predominantly surgical. Primary surgery aims to remove all visible disease and may be considered again at relapse. A large meta-analysis showed a response rate to platinum based chemotherapy of approximately 24% in patients with advanced primary low grade advanced ovarian cancer after upfront surgery, and hence lower than for their high grade serous counterparts (120). The authors concluded that HGSOC and LGSOC differ with respect to chemosensitivity, chemotherapy being of considerably less benefit in patients with LGSOC than patients with HGSOC, growth pattern and outcome following surgery. Hormonal maintenance strategies in LGSOC after completion of platinum based chemotherapy seem to have a survival benefit in retrospective series (121).

International multicentre studies are urgently needed and recruitment to these is important, as is registration of cases onto rare tumour databases to facilitate the study of this rare condition**. (122)**

Mucinous carcinoma of the ovary

True advanced mucinous tumours of primary ovarian origin are rare and effective systemic management / treatment strategies are limited. (Grade B).

Ovarian metastases from primary mucinous tumours of other organs such as GI tract should be excluded. (Grade B)

Mucinous histologies account for 3 – 5% of all ovarian carcinomas. They are typically confined to the ovary at presentation, are large and show a continuum of architectural features including benign, borderline and malignant areas. Confluent and expansile patterns of invasion are often seen, but when an infiltrative pattern is present, the pathologist must be alert to the possibility of a metastatic carcinoma from another site. Invasive mucinous carcinoma with an infiltrative pattern has a more aggressive course than mucinous carcinoma with an expansile pattern. Mucinous carcinomas of the ovary usually exhibit a CK7+/CK20-/CDX2- immunoprofile.

Advanced mucinous tumours, with intra-peritoneal involvement, are unlikely to be of ovarian origin as these are rare. (123) Many of these are Krukenberg tumours or arise from other organs, such as

the appendix. Ovarian tumours metastatic from appendiceal primaries may have morphological features of mucinous borderline tumours and the presence of dissecting mucin in the peritoneal cavity (psuedomyxoma peritonei) favours this diagnosis. Rarely advanced mucinous tumours can arise from an ovarian teratoma.

Surgery with adequate peritoneal staging is the standard treatment for the majority of primary mucinous ovarian tumours. Fertility-sparing surgery should be considered in young women with unilateral disease. The management of advanced true primary ovarian mucinous tumours is challenging, as they are not particularly chemo-responsive. The collection of pathological and clinical data from patients with these rare tumours is vital to allow progress to be made in determining appropriate therapeutic strategies. (124) Patients with advanced disease are usually treated with carboplatin and paclitaxel, although these tumours respond less well to this combination than the more common non-mucinous tumours. mEOC (NCT01081262), a randomised trial comparing carboplatin and paclitaxel, oxaliplatin and capecitabine +/- bevacizumab (a regimen used in gastrointestinal tract cancers) closed early due to poor recruitment.

Where metastasis from the gastro-intestinal (GI) tract must be excluded, bidirectional GI endoscopy should be performed and referral to a GI MDT should be considered.

Other subtypes

Rarer carcinoma subtypes include malignant Brenner tumour, sero-mucinous carcinoma and undifferentiated carcinoma, and transitional cell carcinomas. (125) Mesenchymal tumours that occur in ovaries include endometrial stromal sarcomas and various other sarcomas. In addition, multiple different histological subtypes of cancer can also arise from within mature teratomas, such as squamous cell carcinoma (126) and carcinoid tumours. (127)

Mixed epithelial and mesenchymal tumours

Adenosarcoma is a rare biphasic tumour of the ovary composed of malignant mesenchymal and benign epithelial elements.

Carcinosarcoma is a more common neoplasm, composed of malignant epithelial and mesenchymal elements. Molecular studies indicate that the sarcomatous components of the neoplasms arise from carcinomatous components. High-grade serous carcinomas and carcinosarcomas share several molecular abnormalities including aberrant P53 expression and occasional germline mutation of BRCA2. (36, 37)

Wolffian tumour

Previously termed female adnexal tumour of Wolffian origin (FATWO), this is an uncommon tumour that is presumed to arise from the Wolffian remnants in the adnexal region. The tumour is usually benign and composed of cysts of varying size with sieve like areas admixed with solid and spindled areas.

Small cell carcinoma of the ovary (SCCO)

Four types of small cell carcinoma of the ovary are recognised: hypercalcaemic and pulmonary subtypes (SCCOHT and SCCOPT), as well as a large cell variant, which can be difficult to distinguish from the other two, and the classical carcinoid. Overall these are rare and highly malignant tumours that typically occur in young women. The tumours are usually unilateral with extra-ovarian spread in nearly 75% of cases at the time of presentation. (128) Yong and colleagues found that only 33% of women presenting with stage I SCCO were alive and disease free at an average of 5.7 years' follow up and no patients with advanced disease survived. (129) A diffuse growth pattern, with foci of follicle-like spaces, is typical. The lining cells are monotonous, showing high grade atypia, brisk mitotic activity and necrosis. On immunohistochemistry (IHC), the cells stain positive for WT1 with focal staining for epithelial markers. It has been shown very recently that the cells in SCCOHT are characterised by inactivation of the SMARCA4 gene (encoding the BRG1 protein) resulting in a loss of BRG1 protein expression on IHC. (130) This means that a cohort of the patients with so-called "ovarian" small cell carcinoma have a malignant rhabdoid tumour and maybe a strategy for identifying SCCOHT from SCCOPT and larger cell variants. (131) It is accepted that the patients with small cell ovarian cancer have a dismal prognosis. There maybe some evidence for considering pelvic radiotherapy (RT) for those with early stage disease following surgery but this has not been validated in prospective randomised trials. (132) For those with advanced disease or relapse, chemotherapy schedules are generally extrapolated from those used in small cell lung cancer and generally include a platinum-based agent and etoposide, although more intense treatment strategies have also been investigated. (133) (134)

All of the above more unusual subtypes of ovarian cancers tend to be managed in the same way as serous epithelial ovarian carcinoma, earlier stages clearly benefiting from surgery in the first instance. The introduction of a national rare gynaecological tumour database to assimilate the treatments and outcomes of these patients prospectively will be integral to any progress in managing these rarer malignancies.

Metastatic carcinoma including Krukenberg tumours

Metastasis to the ovary is not an uncommon phenomenon where it may represent the clinical sentinel site of a metastatic cancer. Gross features suggesting metastases are small size, bilaterality, nodular appearance and involvement of the ovarian surface. Microscopic features favouring metastases are an infiltrative growth pattern, stromal desmoplasia, necrosis, hilar and vascular involvement and IHC may assist in determining the primary site of a metastatic mucinous carcinoma. The commonest primary cancer sources (other than from the endometrium or cervix) are colorectal, gastric, pancreaticobiliary and appendicular adenocarcinomas (the appendix may also be the primary site of a borderline mucinous tumour, which progresses rarely to pseudomyxoma peritoneii). Krukenberg tumours are particular ovarian metastases, characterised by bilateral solid ovarian masses, microscopically demonstrating replacement of the ovarian stroma by signet ring, mucinous cells. The primary site is most often gastric or breast, where similar signet ring mucinous cells are seen.

11. Borderline ovarian tumours (BOT)

Complete surgical resection and adequate peritoneal surgical staging has been shown to be associated with a longer PFS in patients with Borderline tumours. (Grade B)

Borderline ovarian tumours with "invasive" peritoneal implants are reclassified as low grade ovarian cancers under the new FIGO classification of 2014.

Pelvic and para-aortic lymph node sampling to stage cases of BOT is not recommended in the absence of bulky lymph nodes. (Grade B)

It is safe for young patients with BOT to receive fertility sparing surgery but given the higher risk of relapse within any remaining ovarian tissue, regular sonographic follow up is recommended. (Grade B)

There is no evidence-based indication for cytotoxic chemotherapy in BOT. (Grade B)

Ovarian epithelial tumour classification is characterised by its unique category of borderline tumours. Although the morphology of these tumours includes no invasive characteristics, clinically their behaviour is not always entirely benign. While borderline endometrioid, clear cell, Brenner tumours and correctly diagnosed mucinous borderline tumours usually behave in benign fashion, the serous and sero-mucinous have a distinct behaviour, which is not always benign.

Serous borderline tumours (SBTs)

These tumours show a typical hierarchical branching pattern lined by cells that show low grade nuclear atypia. When clusters of cells less than 5 mm in greatest dimension, typically with a surrounding clear space, are seen in the stroma, the term microinvasion is applied. Microinvasion is seen more commonly in pregnant patients but the presence of microinvasion does not alter the outcome. (135) Women with stage I disease have the same outcome as the general population, irrespective of microinvasion. (136)

SBTs can also be associated with peritoneal lesions that are termed implants. When the implants are confined to peritoneal/ mesothelial lined surfaces and lack invasion of underlying tissue, they are termed non-invasive implants. Where there is invasion of the underlying fat or muscle, the term invasive implants is used. In some instances, unequivocal invasion is not demonstrable, but the lesion displays the cytological features of invasive implants. (137) The WHO 2014 classification recommends that because these lesions with invasive implants may behave like LGSOC, they should be designated as such. Finally SBTs with micropapillary and microacinar architecture have a greater association with extra-ovarian disease and a higher incidence of recurrence and death from disease than typical SBTs. (138) Morphologically, micropapillae typically lack stromal cores and hierarchical branching. They are composed of cells that are cuboidal, have a high nuclear cytoplasmic ratio and form finger like protrusions that are at least five times longer than broad.

Mucinous borderline tumours (MBTs)

MBTs typically present as large unilateral masses that are confined to the ovary. There are no well-documented cases of MBTs with implants. Adequate sampling of these tumours is crucial, since they are typically heterogenous and can harbour occult foci of carcinoma. (139) MBTs are lined by mucinous epithelium with varying degrees of stratification, tufting and papillary formation. When the lining cells are markedly atypical the term MBT with intraepithelial carcinoma is used. MBT with microinvasion is defined as small foci of microinvasion less than 5 mm in greatest linear dimension. (140) These features do not appear to affect prognosis adversely in stage 1 tumours. (141)

Non-ovarian mucinous tumours, including metastatic ovarian mucinous tumours associated with pseudomyxoma peritonei and metastatic mucinous carcinomas (Krunkenberg tumours) with a deceptive pattern of invasion, are recognized as tumours that can simulate primary MBTs. (142)

Clinical management of borderline ovarian tumours

Complete macroscopic tumour resection should be the aim of all surgery for BOT, with adequate surgical staging especially in apparent stage 1 disease including peritoneal biopsies, cytology and omentectomy (with appendicectomy for mucinous tumours). [Grade B]

A fertility sparing approach in young patients does not preclude adequate peritoneal staging since, even in the presence of peritoneal implants, peritonectomies with preservation of at least one ovary and tube and uterus, can be performed. Adequate surgical staging at initial presentation of the BOT is a defining factor predicting progression-free and overall survival. However, the diagnosis is often made retrospectively following surgery by a non-gynaecological oncologist. Two large retrospective series of women with BOT showed that, higher stage, incomplete staging, residual tumour, and fertility-sparing surgery were independent prognostic factors for recurrence. (136, 143, 144) Patients should be informed about the risks and benefits of completion staging after simple cystectomy or unilateral salpingo-oopherectomy with an incidental finding of BOT. Simple cystectomy in an ovary with BOT carries a risk of relapse and so should be considered mainly for fertility-sparing reasons and after thorough informed consent. (145) Longer-term, the risk of malignant transformation was low overall (~2%), but was found in 30% of those with relapsed disease, although was much less frequent in women under 40 years of age at original diagnosis, compared to those aged over 40 years (12.0% versus 66.7%, $P < 0.001$). Completion surgery could be discussed with women once they have competed their families, even though there are no data to support this having any impact on OS or PFS.

In early stages, with small volume masses and in the absence of extensive peritoneal implants, laparoscopic management is as safe as laparotomy from an oncological point of view. Hysterectomy has no value in complete staging of a patient with BOT. Hysterectomy should be considered if the patient wishes, or for cytoreduction if the uterus is involved with invasive disease. (143)

There is no value in lymph node sampling or dissection in BOT and this should therefore not be routinely performed, although, if bulky lymph nodes are present they should be removed. There is no proven value of cytotoxic chemotherapy in patients with BOT. (143, 146) BOT can relapse decades after the initial diagnosis, and is uncommon in those who have had both ovaries removed. The most

significant risk factor for relapse was the presence of invasive peritoneal implants, however since this group of patients now belongs to the ones with low grade ovarian cancer, the remaining BOT group is prognostically very favourable. For that reason value of follow up in patients with early disease and after bilateral BSO remains unscertain. However, follow up is essential in patients after fertility-sparing surgery since they have a significantly higher risk of relapse in the remaining ovaries. There is no value in the routine CA125 based follow up for BOT patients (143). Relapse of borderline disease should be mainly treated surgically, if disease seems operable, since response to chemotherapy is poor.

12. Support needs for women with ovarian cancer

Women with EOC who require elective surgery in the NHS should have access to a holistic assessment by a clinical nurse specialist (Grade D).

The ovarian cancer pathway is a complex process that includes recognizing abnormal symptoms, worrying that you may have cancer, developing acute symptoms, having tests and investigations, been told that you may have cancer, having cancer confirmed, treatments that include extensive surgery, multiple chemotherapy agents and courses, the potential shortening of ones life, carrying a gene that may affect children and grandchildren, and facing death. Women with ovarian cancer have some or all of these experiences and other related experiences. Women with ovarian cancer report the significant physical and emotional impact of the disease on quality of life (147-151) and the needs of cancer patients often go unmet. (151-153)

Supporting women effectively during the diagnostic, treatment and post treatment phases involves managing the physical, psychological and social impact of the disease and its treatment.

In line with NICE guidelines (2) , women with ovarian cancer should be offered information about their disease (including the stage of the disease, treatment options and prognosis, management of side effects, sexuality, fertility, menopause management, signs and symptoms of recurrence, genetic information, self-help strategies, and dealing with emotions). This should include the amount of detail they want and are able to deal with in a suitable format, including written.

Assessing individual patient need is the cornerstone of patient-centred care. The information and support provided should enable women to make decisions about their care and how it will affect their lives from the time of suspected cancer and diagnosis. Decisions made during this time will impact on immediate treatment and side effects, quality of life and post-treatment consequences.

The National Cancer Survivorship Initiative (NCSI) in England was set up to improve cancer care from the point of diagnosis and recommended the provision of a Holistic Needs Assessment (HNA) for all cancer patients at least at the time of diagnosis and end of treatment. (154) This should include a care plan tailored to individual need. Effectively assessing individual needs and concerns can lead to early interventions and open up communication based on partnership, empowering the patient towards self-management, and the confidence and permission to access available help and support.

The HNA should be a formal process, best led by a framework or tool to ensure that physical, psychological, spiritual, emotional and social domains are considered, and documented to develop an individualised care plan that can be shared with other healthcare professionals, as appropriate. (154) The HNA, together with a treatment summary, a cancer care review and a health and wellbeing

event are key elements of the Recovery Package which, when delivered together, can improve outcomes for people living with and beyond cancer. (155)

Women undergoing surgery may also benefit from being treated within an Enhanced Recovery Programme (ERP), a multimodal perioperative care enhancement protocol designed to improve patient outcomes and speed recovery. (156) There is qualitative evidence to support ERP in women with gynaecological cancer but no evidence to date from high-quality studies specific to gynaecological oncology surgery(157-159), however, data from a colorectal surgery RCT support this approach. (160) The ERP focuses on making sure that patients are active participants in their own recovery process and focuses on four elements:

- Pre-operative assessment, planning and preparation before admission
- Reducing the physical stress of the operation
- Structured approach to immediate post-operative and during (perioperative) management, including pain relief
- Early mobilisation

Effective supportive care involves patient involvement in the care process, and identification and management of individual supportive care needs, to maximise quality of life. Focusing on these needs is a key function of the cancer Clinical Nurse Specialist (CNS). The high-level activities of the cancer CNS can be separated into four main areas; having technical knowledge to oversee and co-ordinate services to personalise the cancer pathway for individual patients, being the key accessible professional for the multidisciplinary team, assessing and alleviating psychosocial suffering including referral as necessary and ensuring services are responsive to patient need. Access to a cancer CNS has been shown to improve patient experience.

13. Appendices

Appendix A

Grades of recommendations

Strength	
A	At least one meta-analysis, systematic reviews or RCT's rated as 1++ and directly applicable to the patient population or A systematic review of RCTs or a body of studies rated as 1+ directly applicable to the patient population and demonstrating consistency of results.
B	Evidence from Level 2++ studies directly applicable to the patient population or extrapolated from level 1 studies.
C	Evidence from Level 2+ studies directly applicable to the patient population or extrapolated evidence from studies rated at 2++.
D	Evidence from Level 3 or 4 studies or extrapolated evidence from studies rated as 2+.

Appendix B

Establishing the diagnosis in secondary care (modified from NICE CG122)

Appendix C

***2014 FIGO ovarian, fallopian tube, and peritoneal cancer staging system and corresponding TNM* (161)**

Stage I. Tumour confined to ovaries or fallopian tube(s)

FIGO staging 2009	**TNM staging**	**Description**
FIGO IA	**T1a-N0-M0**	Tumour limited to one ovary (capsule intact) or fallopian tube; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
FIGO IB	**T1b-N0-M0**	Tumour limited to both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
FIGO IC1	**T1c N0-M0**	Tumour limited to one or both ovaries or fallopian tubes, with surgical spill
FIGO IC2	**T1c-N0-M0**	Tumour limited to one or both ovaries or fallopian tubes, with capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
FIGO IC3	**T1c-N0-M0**	Tumour limited to one or both ovaries or fallopian tubes, with malignant cells in the ascites or peritoneal washings

Stage II. Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer

FIGO IIA	**T2a-N0-M0**	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
FIGO IIB	**T2b-N0-M0**	Extension to other pelvic intraperitoneal tissues

Stage III. Tumour involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes.

FIGO IIIA1 FIGO IIIA1(i) FIGO IIIA1(ii)	**T1/T2-N1-M0**	Positive retroperitoneal lymph nodes only (cytologically or histologically proven) Metastasis up to 10 mm Metastasis more than 10 mm
FIGO IIIA2	**T3a2-N0/N1-M0**	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
FIGO IIIB	**T3b-N0/N1-M0**	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
FIGO IIIC	**T3c-N0/N1-M0**	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)

Stage IV. Distant metastasis excluding peritoneal metastases

FIGO IVA	Any T, any N, M1	Pleural effusion with positive cytology
FIGO IVB	Any T, any N, M1	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Appendix D

Risk of Malignancy Index I (RMI I) calculation

RMI I combines three pre-surgical features: serum CA125 (CA125), menopausal status (M) and ultrasound score (U). The RMI I is a product of the ultrasound scan score, the menopausal status and the serum CA125 level (IU/ml). (31)

RMI I = U x M x CA125

The ultrasound result is scored 1 point for each of the following characteristics: multilocular cysts, solid areas, metastases, ascites and bilateral lesions.

U = 0 (for an ultrasound score of 0)

U = 1 (for an ultrasound score of 1)

U = 3 (for an ultrasound score of 2–5)

The menopausal status is scored as 1 = pre-menopausal and 3 = post-menopausal.

The classification of 'post-menopausal' is a woman who has had no period for more than 1 year or a woman over 50 who has had a hysterectomy.

Serum CA125 is measured in IU/ml and can vary between 0 and hundreds or even thousands of units.

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